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Abstract

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Project Title:	High-Throughput Screen for Antagonists of the Plasmodial Surface Anion Channel (PSAC)

Abstract: *DESCRIPTION (provided by applicant):* We propose a high-throughput screen for antagonists of a novel ion channel on P. falciparum-infected red blood cells (RBCs). This channel, the plasmodial surface anion channel (PSAC), is highly conserved in all studied human, rodent, and primate malaria models. Because PSAC dramatically increases RBC permeability to amino acids, purines, vitamins, and precursors for phospholipid biosynthesis (all required for in vitro parasite growth), it likely serves an essential role in intraerythrocytic parasite nutrient acquisition. Our high-throughput screen aims to identify high affinity, specific PSAC antagonists that kill parasites by interfering with nutrient uptake. PSAC has already been recognized as an important antimalarial drug target by the Medicines for Malaria Venture, a nonprofit organization created to discover, develop and deliver new antimalarial drugs through effective public-private partnerships. With MMV support, the Principal Investigator has initiated collaborations with academic and pharmaceutical screening facilities. Our previous high throughput screens, carried out in 384-well and in 3,456-well formats, identified high affinity antagonists that have provided insights into PSAC structure and biological role. Some antagonists identified may be starting points for collaborative drug discovery programs. Lay language statements: The deadly malaria parasite, Plasmodium falciparum, lives and grows within human blood cells. Because it has a high metabolism, it must acquire nutrients from serum. It uses an unusual ion channel known as the Plasmodial Surface Anion Channel (PSAC), induced on the blood cell membrane by the parasite, to facilitate nutrient uptake. We propose to find inhibitors of PSAC by screening large collections of drug-like molecules. Identified inhibitors may be developed into desperately needed antimalarial drugs.

Thesaurus Terms: high-throughput screening, HTS, P. falciparum, plasmodial surface anion channel, PSAC, malaria, phospholipid biosynthesis, intraerythrocytic parasite nutrient acquisition, 384-well format, 3,456-well format, Plasmodium falciparum, nutrient uptake

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